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Epidemiology of community-onset *Clostridium difficile* infection in a community in the South of England

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Abstract
Background and aims: Clostridium difficile infection (CDI) has traditionally been considered a hospital acquired infection but there are a rising number of infections in the community. This study estimates the prevalence of community-onset CDI (CO-CDI), defined as onset of symptoms in a community setting and outside the hospital, and examines the risk factors for CO-CDI in 2—64 year-olds.
Methods: A standard questionnaire was used to retrospectively obtain information on the CDI risk factors of 58 cases of CO-CDI diagnosed between 1st April 2008 and 31st March 2009 in a community in the South of England. Each case was reviewed for the presence of 'established' risk factors for CDI, i.e., age $\geq$65 years, in-patient hospital stay, and recent (within $\leq$4 weeks) receipt of broad spectrum antibiotics, and other, 'non-established' risk factors for CDI, such as exposure to antibiotics more than 4 weeks preceding symptom onset, out-patient and day-surgery hospital exposure, contact with a hospitalised patient, and travel outside of the UK.
Results: Fifty-eight cases of CO-CDI were diagnosed among a total community population of 418,000, representing an estimated prevalence of CO-CDI of 1.29 per 10,000. All 58 cases were successfully contacted, representing a 100% response rate. Four cases were excluded from further analysis due to co-infection with *Salmonella* spp. and *Campylobacter* spp. Cases were more likely to be female, aged between 31 and 40 years, and present in the spring season (March—May), 2009. 46.3% (25/54) of cases had established risk factors for CDI, 20.4% (11/54) had non-established risk factors, 16.7% (9/54) had no risk factors and in the remaining 16.7% (9/54), available information was insufficient to classify by risk factor category.

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Conclusions: This study suggests that CDI should be included in the differential diagnosis of community-onset diarrhea in patients with or without established risk factors for CDI.

1. Introduction

Clostridium difficile (*C. difficile*) infection (CDI) has traditionally been considered a nosocomial infection. Established risk factors for CDI include age over 65 years [1]; recent (within ≤4 weeks) in-patient hospital or long-term care facility (LTCF) stay [1]; recent (within ≤4 weeks) use of antimicrobials [1—6]; concomitant use of multiple antibiotics [1]; immunosuppression [7]; previous CDI [1]; and underlying medical conditions, especially those affecting the colonic flora [1,5,7—10]. Recently CDI has been increasingly observed in the community setting and in individuals without established risk factors [2,6]. Although reasons for this changing epidemiology are not fully understood, increasing host susceptibility due to novel risk factors, higher community total antibiotic consumption, emergence of new epidemic *C. difficile* strains, and a growing reservoir of asymptomatic carriers or colonised patients and animal reservoirs in the community are the likely explanations. [1].

CDI-related definitions in the literature vary. A case of healthcare-associated CDI is defined as one in which symptom onset occurs more than 48 h after admission to, or within 4 weeks of discharge from, a healthcare facility [12]. A case of community-associated CDI (CA-CDI) is defined as one in which symptom onset occurs within 48 h of admission and over 4 weeks following discharge from a healthcare facility [12]. However, other definitions and cut-off periods continue to be used [5,13]. In this paper we used 'community-onset CDI' (CO-CDI), to define a case of CDI with symptom onset in the community.

The aims of our study were to estimate the prevalence of CO-CDI from diarrheal samples submitted from a community setting, and to identify risk factors for CDI in individuals previously considered to be at low risk.

2. Methods

Our study represented a retrospective, descriptive epidemiology of CO-CDI in a community in Berkshire, in the South of England. The Royal Berkshire NHS Foundation Trust (RBFT) microbiology laboratory tested diarrheal samples (defined as stool taking the shape of its container) using the *C. difficile* toxins A and B enzyme immunoassay. Diarrheal stools received from all individuals aged over 2 years were tested for *C. difficile* and positive cases were reported to the UK Department of Health under the Healthcare-Associated Infections mandatory surveillance scheme.

Our study looked at cases of CDI in 2—64-year-old individuals from the community diagnosed by the RBFT microbiology laboratory between 1 April 2008 and 31 March 2009. Asymptomatic carriage of *C. difficile* is common in children aged up to 2 years, and children below this age were therefore not included. The upper age limit of 64 years was chosen as age ≥65 years was considered an established risk factor for developing CDI, and the aim of the study was to explore risk factors in 2—64 year-old individuals previously considered to be at low risk. Individuals (or parents/carers in cases of children) who tested positive for *C. difficile* were contacted by telephone by a member of the West Berkshire community infection control team and information on age, symptoms, possible risk factors, medical history and drug history was collected using a standard proforma (see Appendix A).

CO-CDI cases were categorised into four groups based on the presence and type of CDI risk factors: established; non-established; none; and unknown. A case with established risk factors had one or more of the following: a history of receipt of antibiotics in the 4 weeks preceding symptom onset; in-patient hospital or LTCF stay in the 8 weeks preceding symptom onset; underlying immunosuppression; regular use of proton pump inhibitors (PPI); underlying gastrointestinal conditions such as inflammatory bowel disease; and a history of CDI. Non-established risk factors were defined as factors for which an association to CDI has been proposed but not formally established in the literature. A case of CO-CDI with 'non-established' risk factors had one or more of the following: a history of antibiotic use over 4 weeks preceding symptoms; an out-patient or a day-surgical hospital attendance in the 8 weeks preceding symptoms; contact with a recently hospitalised patient; and travel outside of the UK within the preceding 8 weeks. A case with neither

'established' nor 'non-established' risk factors was classified as having 'none'. Finally, a case where information on risk factors was either insufficient or unclear was classified as 'unknown'. Collation and basic statistical analyses of the results were carried out with Microsoft Excel.

3. Results

In the period between 1st April 2008 and 31st March 2009, 3743 2—64 year-olds in the community were tested for CDI by the RBFT microbiology laboratory. Fifty-eight (1.5%) cases of CO-CDI were identified. All 58 cases were successfully contacted by telephone, giving a response rate of 100%. Four of the 58 cases tested positive for additional infectious organisms (three tested positive for *Campylobacter* spp.; one tested positive for *Salmonella* spp.) indicating co-infection; these four cases were excluded from further analysis. Among a total Berkshire West population of 418,000 2—64 year-olds, this equates to a CO-CDI prevalence of 1.29 per 10,000 population. Overall, 25 (46.3%) of 54 cases had established risk factors for CDI; 11 cases (20.4%) had non-established risk factors; 9 (16.7%) cases had no risk factors; and insufficient information on risk factors was obtained for the remaining 9 (16.7%) cases.

A summary of the sex, age and seasonal distribution of cases is shown in Table 1. CO-CDI was more common in females than males (63% of positive samples were from females vs. 37% from males). Cases were most common among the age group 31—40 years (13 cases; 24.1%), followed by 51—60 years (11 cases; 20.4%). The number of cases peaked during the period March—May 2009, which accounted for 40.7% of total annual activity. The summer period of June-August 2009 saw the least activity (8 cases; 14.8% of annual activity).

Table 2 and Fig. 1 show the distribution of risk factors. Amongst the 25 cases with established risk factors, receipt of antibiotics within the preceding 4 weeks was the most common risk factor, identified in 31.5% (17/54) of cases. An in-patient hospital or LTCF stay within the preceding 8 weeks was identified in 13.0% (7/54) of cases. Less common established risk factors were underlying immunosuppression, use of PPIs, underlying gastrointestinal disease, and history of CDI. Of the 11 cases with non-established risk factors, 4 had had an out-patient hospital attendance or a day-case surgical procedure within the 8 weeks preceding symptom onset, and a further 4 had had contact with a recently hospitalised patient. Three cases had travelled outside of the UK in the preceding 8 weeks, and 2 had received antibiotics over 4 weeks preceding symptom onset.

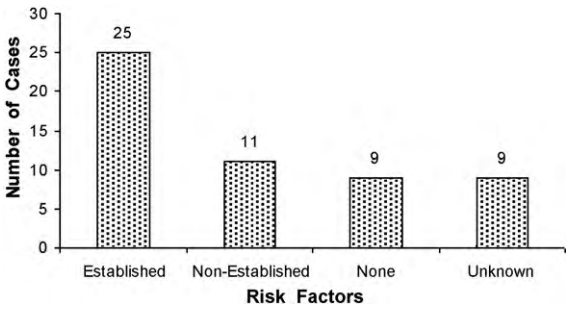

Fig. 1 Presence of risk factors in cases of CO-CDI.

4. Discussion

Our study suggests a prevalence rate of CO-CDI of 1.29 cases per 10,000 population of 2—64 year-olds in a community in the South of England. This is comparable to figures of 1.1 per 10,000 from one other UK study [16] but significantly lower than the findings of some other studies [6].

CDI in young, healthy females is an important finding of our study and must be emphasised strongly. The finding that more female than male samples tested positive for CDI again reflects the findings of other studies [12,15]. Reasons for this gender difference are unclear but differences in symptom interpretation, healthcare-seeking behaviour, and referral for specialist treatment and investigations may play a role [17]. More research is needed to investigate these possibilities further.

Less than half (46.3%) of all cases of CO-CDI were associated with established risk factors. This was a significant finding and suggests that CDI should be considered as a differential diagnosis even in the absence of established risk factors. Our findings suggest that out-patient hospital exposure, day-case surgical procedures, contact with recently hospitalised individuals, contact with known cases of CDI, and travel outside of the UK might be associated with increased risk of CO-CDI. Larger and more systematic studies are needed to investigate these possible associations further.

Our study had a number of limitations. Importantly, our figure of 1.29 cases of CO-CDI per 10,000 population represented only the minority of all cases in a population who sought medical care and submitted stool specimens for testing. Moreover, reported cases might differ systematically from unreported cases [18] and our sample might be biased towards cases of CO-CDI with more severe symptoms. The Health Protection Agency Primary

Table 1 Summary of case characteristics (sex, age and month of presentation).

	Number	Percent of total
No. of patients (2—64 years) tested	3,743	
No. of cases positive for *C. difficile*	58	
Cases excluded[a]	4	
Total cases classified as CDI	54	1.4
Sex		
Male	20	37.0
Female	34	63.0
Age (years)		
2—10	6	11.1
11—20	4	7.4
21—30	9	16.7
31—40	13	24.1
41—50	7	13.0
51—60	11	20.4
61—65	3	5.6
Unknown	1	1.9
Month of presentation		
March—May	22	40.7
June—August	8	14.8
September-November	14	25.9
December-February	10	18.5

[a] Four cases excluded due to co-infection with another infectious organism.

care guidance [19] recommends testing for CDI in specific epidemiological settings, including recent antibiotic or PPI use and recent hospitalisation, which might introduce patient selection bias for laboratory investigation of CDI. Apart from consistency of stool, there are no standard selection criteria for CDI testing [20]. Our local laboratory protocol included CDI testing of diarrheal stools from all patients over 2 years of age.

The total number of cases was small, leading to less certainty around estimates. A significant (16.7%) proportion of questionnaires were incomplete or contained insufficient information for analysis, adding further uncertainty to the interpretation of results. The retrospective nature of the study raises the possibility of recall bias. Ideally, controls (individuals in the community with CDI-negative diarrhea) would also have been ques-

Table 2 Presence of risk factors among cases of CA-CDI.

	Number	Percent of total[c]
Established Risk factors[b]	25	46.3
Recent (within 4 weeks of symptom onset) use of antibiotics	17	31.5
Recent (within 8 weeks of symptom onset) overnight hospital/LTCF stay	7	13.0
Immunosuppression	2	3.7
Use of PPI	1	1.9
Underlying GI disease	1	1.9
Previous CDI	1	1.9
Non-established risk factors[b]	11	20.4
Out-patient or day-case surgical hospital attendance	4	7.4
Contact with a recently hospitalised patient	4	7.4
Travel outside the UK	3	5.6
Use of antibiotics (>4 weeks prior to symptom onset)	2	3.7
No risk factors	9	16.7
Unknown/insufficient information	9	16.7

[b] Some cases had more than 1 risk factor.
[c] Calculated as percentage of total cases ($n = 54$).

tioned, but time and resources did not allow for this. Data collection was limited by the standard questionnaire, which did not specifically ask about other potential (non-established) risk factors for CDI. Contact with children aged less than 2 years, for example, has been proposed as a possible risk factor for CDI in the community but was not explicitly asked about in our study questionnaire.

Although it has been recommended that testing for CDI in the community of all cases of diarrhea among patients aged $\geq$2 years should be included in the laboratory protocols for the investigation of diarrhea [12], the evidence from this study is insufficient in arguing the case either for or against this. More research and consideration of costs and disease outcomes are required to accurately assess whether testing for CDI significantly affects case management and whether it should be extended to all patients $\geq$2 years. Finally, we recommend the development of a more stringent definition of the term 'community-associated' CDI. Cut-off periods may need broadening and risk factors re-examining in the light of new evidence. In the meantime, community-onset CDI is a more accurate descriptor of diarrhea in the community testing positive for CDI.

5. Conclusion

This study demonstrates that prevalence of CO-CDI in this community remains low. Receipt of antibiotics is the single most important risk factor for CO-CDI. Nevertheless, CDI should be considered as a cause of diarrhea in patients even in the absence of traditional risk factors for the disease. Monitoring and active surveillance of all cases of *C. difficile* locally, nationally and internationally is needed continually improve our understanding of the changing epidemiology of the disease.

Conflict of interest

Funding: None.

Competing interests: None.

Ethical approval: None required as questionnaires are filled in retrospectively on every case of CDI as part of mandatory CDI surveillance.

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Appendix A. *Clostridium difficile* Audit Tool

Patient name:	NHS Number:
DOB/Age:	GP Surgery:
Has the patient had any recent acute hospital admissions/visits (please include dates and facility):	
This CDAD episode definition: CDT[a] only/CDAD[b]/PMC[c]	
If PMC, on basis of: Sigmoidoscopy/SIRS/AXR	
Toxic megacolon: Yes/No	Is this episode a relapse[d]? Yes/No
Symptoms	
Date of onset:	Date of CDT positive:
Previous CDT: Yes/No	
Isolation: Yes/No	Date of isolation:
Comment:	
Treatment	
Initial treatment: None/Metronidazole/PO Vancomycin	
Start/stop date:	Was treatment successful? Yes/No
Outcome: Refractory[e]/Relapse[f]	
Adjunctive treatment	
Vancomycin PO: Yes/No	Steroids: Yes/No
Metronidazole: Yes/No	IV Ig: Yes/No
Cholestyramine: Yes/No	

Appendix A (*Continued*)

Drug History

Chemotherapy including steroids: Yes/No

Antibiotics: Yes/No — Name:

Dose: — Route:

Start date: — Stop date:

PPIs: Yes/No

Other diagnoses:

Colitis: Yes/No — GI Cancer: Yes/No

Diverticulitis: Yes/No — Other infective diagnoses:

Any additional notes:

[a] CDT only: positive *C. difficile* toxin assay.
[b] CDAD: cases in which specimens were taken before admission of the patient to hospital or within 48 h of admission.
[c] PMC: pseudomembranous colitis as based on evidence of severe colitis (abdominal or radiological signs).
[d] Initial improvement and/or resolving of symptoms followed by renewed onset of symptoms.
[e] No response to treatment.
[f] Initial improvement and/or resolving of symptoms following treatment, followed by renewed onset of symptoms.

References

[1] Owens RC, Donskey CJ, Gaynes RP, Loo VG, Muto CA. Antimicrobial-associated risk factors for *Clostridium difficile* infection. Clinical Infectious Diseases 2008;46:19—31.

[2] T. LaMont, Epidemiology, microbiology, and pathophysiology of Clostridium difficile infection, UpToDate 2008. Available from: http://www.uptodate.com/patients/content/topic.do?topicKey=~PcZvVbHmEOfOyw [last accessed 26.10.09].

[3] Bignardi GE. Risk factors for *Clostridium difficile* infection. Journal of Hospital Infections 1998;40:1—15.

[4] Johnson S, Samore MH, Farrow KA, et al. Epidemics of diarrhea caused by a clindamycin-resistant strain of *Clostridium difficile* in four hospitals. New England Journal of Medicine 1999;341:1645.

[5] Delaney JAC, Dial S, Barkun A, Suissa S. Antimicrobial drugs and community-acquired *Clostridium difficile*-associated disease, UK. Emerging Infectious Diseases 2007;13:761—3.

[6] Bauer MP, Goorhuis A, Koster T, Numan-Ruberg SC, Hagen EC, Debast SB, et al. Community-onset *Clostridium difficile*-associated diarrhea not associated with antibiotic usage: two case reports with review of the changing epidemiology of *Clostridium difficile*-associated diarrhea. The Netherlands Journal of Medicine 2008;66:207—11.

[7] Monaghan T, Boswell T, Mahida YR. Recent advances in *Clostridium difficile*-associated disease. Gut 2008;57:850—60.

[8] Fraser TG, Fatica C, Gordon SM. Necessary but not sufficient: a comparison of surveillance definitions of *Clostridium difficile*-associated diarrhea. Infection Control and Hospital Epidemiology 2009;30:377—9.

[9] Dial S, Kezouh A, Dascal A, Barkun A, Suissa S. Patterns of antibiotic use and risk of hospital admission because of *Clostridium difficile* infection. Canadian Medical Association Journal 2008;179:767—72.

[10] Centers for Disease Control and Prevention (CDC). Severe *Clostridium difficile*-associated disease in populations previously at low risk. Morbidity and Mortality Weekly Report 2005;54:1201—5.

[12] Department of Health and Health Protection Agency. *Clostridium difficile* infection: how to deal with the problem. London: Department of Health; 2009.

[13] Kuijper J, van Dissel JT. Commentary: spectrum of *Clostridium difficile* infections outside health care facilities. Canadian Medical Association Journal 2008;179:747—8.

[15] Centers for Disease Control and Prevention (CDC). Surveillance for community-associated Clostridium difficile. Morbidity and Mortality Weekly Report 2008;57:340-3.

[16] Food Standards Agency. A report of the study of infectious intestinal disease in England. London: The Stationery Office; 2000.

[17] Adamson J, Ben-Shlomo Y, Chaturvedi N, Donovan J. Ethnicity, socio-economic position and gender — do they affect reported health-care seeking behaviour? Social Science and Medicine 2003;57:895—904.

[18] Tam C, Rodrigues L, O'Brien SJ. The study of infectious intestinal disease in England: what risk factors for presentation to general practice tell us about potential for selection bias in case-control studies of reported cases of diarrhoea. International Journal of Epidemiology 2003;32:99—105.

[19] Health Protection Agency, Infectious Diarrhoea — the role of microbiological examination of faeces. Available from: http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/PrimaryCareGuidance/ [accessed 21.06.10].

[20] National *Clostridium difficile* Standards Group. Report to the Department of Health. Journal of Hospital Infections 2004;56:1—34.